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METHOD OF TREATMENT

This invention relates to a method of treating the weight of patients and is particularly concerned with a method of treating the weight of patients suffering from psychoses.

5 Schizophrenia is a chronic and debilitating illness that affects approximately 1% of the population worldwide. For many years, conventional antipsychotic agents have been widely used to treat schizophrenia; however, they are associated with undesirable motor symptoms (extrapyramidal symptoms [EPS]) such as akathisia, dyskinesia, bradykinesia and parkinsonism, which are known to contribute to poor compliance with treatment. Such  
10 adverse effects of the older, typical antipsychotics caused a great deal of distress to patients but were tolerated as being inevitable in the treatment of psychotic symptoms. Even so, studies have suggested that 40% of patients stopped taking their medication within 1 year and 75% of patients stopped within 2 years (Perkins, 1999, J. Clinical Psychiatry 60 (suppl. 21), pp 25-30).

15 Many of the newer, atypical antipsychotic agents have an improved tolerability profile. With the resulting diminution in prevalence of the very debilitating EPS, more attention is being focused on other side effects of these agents, including a propensity to induce weight gain, seen with most atypical antipsychotics to a greater or lesser degree (Wirshing et al, 1999, J. Clinical Psychiatry 60: 358-63). In some cases, this may adversely affect patients' quality  
20 of life and possibly treatment compliance.

It has been recognized for more than 40 years that there is an association between antipsychotic medication and weight gain. In the past, weight gain has been linked to efficacy of antipsychotic medication, with research linking a positive outcome with increased weight. However, more recent research has shown this not to be the case (Umbricht et al, 1994, J.  
25 Clinical Psychiatry 55 (suppl. B): 157-60; Bustillo et al, 1996, American J. Psychiatry 153: 817-9).

Weight gain is associated with increased morbidity and mortality from a wide range of conditions including hypertension, coronary heart disease, cerebrovascular disease, type 2 diabetes mellitus, various cancers, sleep apnea and respiratory problems. It is also linked with  
30 morbidity related to the disease being treated itself. Studies have shown that the side effect of weight gain causes relatively more distress than many of the other common side effects associated with antipsychotic medication (Weiden, 1999). If weight gain is considered by the

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patient to be unacceptable, compliance with the antipsychotic may be reduced and a worsening of the psychotic condition may ensue.

The extent to which each of these antipsychotic agents is associated with weight gain varies considerably (Allison et al, 1999, Am. J. Psychiatry 156: 1686-96; Wirsching et al, 1999). Weight gains of 3.99, 3.51 and 2.00 kg have been estimated following 10 weeks treatment with clozapine, olanzapine and risperidone, respectively (Allison et al, 1999).

Simansky et al, (Am. Psychiatry Association Meeting, Washington, USA, May, 1999) report on weight gains associated with treatment using ziprasidone, risperidone, quetiapine, olanzapine or clozapine. They confirm that the largest weight gains are associated with treatment using olanzapine or clozapine. They report that quetiapine is associated with a weight gain greater to that seen with risperidone and greater than that seen with ziprasidone. However, this report is based on an extrapolation to a ten week period based on an estimate at week 6 of treatment.

We have unexpectedly found that quetiapine is associated with a small mean weight increase in the first 5-6 weeks of treatment with little further mean change observed over 12 months of treatment. Actual mean weight increase for quetiapine treated patients differs markedly from the extrapolated figures reported by Simansky et al.

According to the present invention, there is provided a method of treating the weight of a patient which comprises administering an effective amount of quetiapine or a pharmaceutically acceptable salt thereof to said patient.

In another aspect, the present invention provides quetiapine or a pharmaceutically acceptable salt thereof for use in treating the weight of a patient.

In yet a further aspect, the present invention provides the use of quetiapine or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating the weight of a patient.

Quetiapine is 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1,4]thiazepine. This compound pharmaceutically acceptable salts thereof and use in treating schizophrenia are described in granted European Patent No. EP 240,228.

In particular, the patient is suffering from psychoses.

It is well recognized that there is a link between obesity and diabetes, especially type II diabetes, and that moderate to severe obesity increases the risk of developing diabetes. It is also widely accepted that weight loss results in metabolic improvement and hence in glycaemic control and insulin sensitivity which in turn give rise to improvements in

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cardiovascular risk factors. This is reported by, for example, Bosello et al, Int. J. of Obesity, (1997) 21, Suppl 1, S10-13.

Weight gain in patients is generally undesirable but is more so in patients who are diabetic or who are at risk from developing diabetes.

5 Accordingly, the present invention further provides a method of treating the weight of a patient who is exhibiting diabetes or is at risk from developing diabetes which method comprises administering an effective amount of quetiapine or a pharmaceutically acceptable salt thereof to said patient. In particular, the patient is suffering from psychoses.

10 In an alternative aspect of the present invention, there is also provided a method of treating psychoses in a patient who is diabetic or who is at risk from developing diabetes which method comprises administering an effective amount of quetiapine or a pharmaceutically acceptable salt thereof to said patient.

In particular the patient is diabetic, that is exhibiting one or more of the symptoms of diabetes.

15 Quetiapine and pharmaceutically acceptable salts thereof are particularly effective in inducing weight loss in patients who have tended to gain weight when treated with other antipsychotics such as clozapine or olanzapine, in particular clozapine. Under such circumstances, quetiapine or pharmaceutically acceptable salts thereof may reverse at least part of any weight gained as a result of treatment with the antipsychotic such as clozapine or  
20 olanzapine, in particular clozapine.

In a particular aspect, the dosage of the other antipsychotic agent, such as clozapine or olanzapine, is decreased during treatment with quetiapine or pharmaceutically acceptable salt thereof.

25 The method of treatment of the present invention relates to short term (5-6 weeks), medium term (1-6 months) and long term (6 months-2 years or more) treatment, and is particularly valuable in medium term and long term treatment.

Quetiapine may be administered as the compound, 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1.4]thiazepine or may be administered in the form of a pharmaceutically acceptable salt. Examples of suitable salts include, for example, chloride,  
30 maleate, fumarate, citrate, phosphate, methane sulphonate and sulphate salts. Preferred salts include fumarates and a particularly preferred salt is the hemi-fumarate.

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It is generally preferred that 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperaziny)-dibenzo[b,f][1.4]thiazepine is administered in the form of a pharmaceutically acceptable salt, and in particular a fumarate (2:1) salt.

In the treatment of the diseases and conditions mentioned above quetiapine or a pharmaceutically acceptable salt may be administered orally or parenterally in a conventional dosage form such as tablets, pills, capsules, injectables or the like. The dosage in mg/kg of body weight of the compound used to treat mammals will vary according to the size of the mammal and particularly with respect to the brain/body weight ratio. In general, a higher mg/kg dosage for a small animal such as a dog will have the same effect as a lower mg/kg dosage in an adult human. A minimum effective dosage for quetiapine or a pharmaceutically acceptable salt thereof will be at least about 1.0 mg/kg of body weight per day for mammals with a maximum dosage for a small mammal such as a dog, of about 200 mg/kg per day.

For humans, a dosage of about 1.0 to 40 mg/kg per day will generally be effective.

Typically, a dosage of about 25mg to 800mg per day will generally be effective.

Usually, a dosage of about 150mg to 750mg per day will be administered, with a convenient dosage being about 300mg per day. In some groups of patients a lower dosage may be preferred such as 100mg per day. The dosage can be given once daily or in divided doses, for example, 2 to 4 doses daily. The dose may be conventionally formulated in an oral or parenteral dosage form by compounding 25 to 500 mg per unit dosage of conventional vehicle, excipient, binder, preservative, stabilizer, flavor or the like as called for by accepted pharmaceutical practice, for example, as described in US Patent 3,755,340.

Quetiapine or a pharmaceutically acceptable salt may be used in pharmaceutical compositions as the sole active ingredient or may be contained in a pharmaceutical composition together with one or more other active ingredients, or it may be co-administered with one or more known drugs.

Quetiapine or a pharmaceutically acceptable salt may be administered in conjunction with one or more other agents useful for treating diabetes.

Quetiapine or a pharmaceutically acceptable salt may be administered in conjunction with one or more other agents useful for treating psychoses.

As indicated above, where quetiapine or a pharmaceutically acceptable salt is administered in conjunction with another agent it may be administered simultaneously, sequentially or separately with that other agent or agents. Thus, as indicated above, quetiapine

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or a pharmaceutically acceptable salt may be formulated with the other agent or agents or may be presented as a separate formulation.

Thus, in one aspect of the present invention, there is provided a pharmaceutical composition comprising quetiapine or a pharmaceutically acceptable salt and an agent known for treating diabetes together with a pharmaceutically acceptable diluent or carrier.

In a further aspect there is provided a pharmaceutical composition comprising quetiapine or a pharmaceutically acceptable salt and an agent for treating diabetes for simultaneous, sequential or separate administration.

The preparation of 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1,4]thiazepine and its pharmaceutically acceptable salts is described in, for example, granted European Patents Nos. EP 240,218; EP 282,236 and in International Patent Application No. PCT/GB98/02260. This compound is commercially available under the generic name quetiapine fumarate.

The invention will now be illustrated with reference to the following, non-limiting examples in which quetiapine was used as the fumarate (2:1) salt..

### Example 1

Body weight data were collected for a group of 65 randomly-selected schizophrenic patients who were on clozapine initially (200 - 800 mg/day for 6 months) and then had quetiapine added to their therapy. Weights were recorded monthly, and status of diabetes follow-up was also performed. Clozapine dosages were reduced as quetiapine was added. The duration of treatment with quetiapine was 10 months. Data were extracted from retrospective chart review of 65 patients who were prospectively assigned to clozapine-quetiapine therapy. All 65 patients showed weight loss ranging from 0.5 to 23 lbs, with a mean loss of 3.98 lbs, after the first month of combination treatment; the quetiapine dose at one month ranged from 200 - 800 mg/day. The improvement continued throughout the 10-month study period. Total weight loss ranged from 1 to 41 lbs, with a mean loss of 9.2 lbs over the course of the study. Twenty per cent of patients developed diabetes during clozapine monotherapy and each showed significant improvement of diabetes with addition of quetiapine, as assessed through monthly blood monitoring and clinical improvement.

Thus, an unexpected clinical effect of quetiapine is its apparent propensity to induce weight loss and help with diabetes management in patients who gain weight and develop diabetes on clozapine.

**Example 2**

427 patients (277 male; 150 female) were treated with quetiapine monotherapy during controlled and open-label extension studies for up to 3.5 years and weight changes were monitored at specified time intervals throughout this period. The patients were in the age range 18-75 with a mean age of 37.3 years.

Patients were grouped using an observed cases approach within specified time intervals. Data on patients who received quetiapine monotherapy during the controlled portion of the trial and/or quetiapine during the open-label extension period are reported. Data were obtained for 30% of patients for at least one year.

Over the first 4 weeks, a mean weight loss of 0.36 Kg (n=17) was recorded. At subsequent time intervals weight changes were -0.17 kg (n=49) at weeks 5-8; +1.58 kg (n=171) at weeks 9-13; +0.29 kg (n=153) at weeks 14-26; +1.73 kg (n=128) at weeks 27-39; -1.47 kg (n=37) at weeks 40-52; +2.00 kg (n=116) at weeks 53-78; +3.43 kg (n=64) at weeks 79-104; +3.45 kg (n=44) at weeks 105-130 and +0.36 kg (n=9) at weeks 131-156. Patients received a mean quetiapine dosage of approximately 475 mg/day after one year of open-label treatment. Only one patient withdrew from the open-label study due to an adverse event of weight gain.

Thus, an unexpected clinical effect of quetiapine is its apparent capability of being associated with minimal weight gain unlike olanzapine and clozapine.

**Example 3**

The following illustrates representative pharmaceutical dosage forms containing the compound 11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl)-dibenzo[b,f][1,4]thiazepine fumarate (2:1).

**(a) Tablet**

	<u>mg/tablet</u>
Quetiapine fumarate .....	50.0
Mannitol, USP .....	223.75
Croscarmellose sodium .....	6.0
Maize starch .....	15.0
Hydroxypropylmethylcellulose (HPMC),	2.25
Magnesium stearate .....	3.0

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(b) Capsule

Quetiapine fumarate.....	10.0
Mannitol, USP.....	488.5
Croscarmellose sodium.....	15.0
5 Magnesium stearate.....	1.5

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

10 A preferred formulation is that available commercially as quetiapine fumarate.

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